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## **Induction or exacerbation of psoriasis in patients with Crohn's disease under treatment with anti-TNF antibodies**

Barthel, Christiane ; Biedermann, Luc ; Frei, Pascal ; Vavricka, Stephan R ; Kündig, Thomas ; Fried, Michael ; Rogler, Gerhard ; Scharl, Michael

**Abstract:** BACKGROUND AND AIMS: Paradoxically, psoriasis or psoriasiform skin lesions induced or exacerbated by anti-TNF antibodies have been described. Here, we report a series of 13 novel cases featuring exacerbation or occurrence of psoriatic skin lesions induced by anti-TNF antibodies in patients with Crohn's disease (CD). METHODS: We performed a systematic analysis of exacerbation or occurrence of psoriasis or psoriasiform skin lesions induced by anti-TNF antibodies in an inflammatory bowel disease patient cohort at the University Hospital Zurich. RESULTS: We identified 13 CD patients who developed psoriasis or psoriasiform lesions while receiving anti-TNF therapy. 10 of the 13 patients were female with an average age of 26.9 years at diagnosis. 11 of the 13 patients had a complicated disease. The mean time of clinical latency between diagnosis and onset of psoriasis was about 9.4 years, and the time between the beginning of all biological infusions and the onset of psoriasis was about 7 months. 7 of the 13 patients received infliximab, 3 adalimumab, and 3 certolizumab pegol at onset of psoriasis. In most of the cases, anti-TNF therapy was changed or discontinued and skin lesions improved. CONCLUSION: Most of our described patients featured a complicated disease course of CD and had an improvement of the rash after changing the anti-TNF therapy.

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# **Induction or exacerbation of psoriasis in patients with Crohn's disease under treatment with anti-TNF antibodies: 13 new cases and a review of literature**

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## **ABSTRACT (250; max. 250)**

*Background:* Anti-TNF agents have acquired a prominent place in the treatment of IBD and psoriasis. Paradoxically, psoriasis or psoriasiform skin lesions induced or exacerbated by anti-TNF antibodies have been described. Here, we report a series of 13 novel cases featuring exacerbation or occurrence of psoriatic skin lesions induced by anti-TNF antibodies in patients with Crohn's disease (CD).

*Methods:* We performed a systematic analysis of exacerbation or occurrence of psoriasis or psoriasiform skin lesions induced by anti-TNF antibodies in an IBD patient cohort at the University Hospital Zürich and a critical literature review.

*Results:* We identified 13 CD patients who developed a psoriasis or psoriasiform lesions while receiving anti-TNF-therapy. 10 of 13 (77%) were female with an average age of 26.9 (18-54) years at diagnosis. 11 of 13 patients (85%) had a complicated disease characterized either by stenosis or fistulae. The mean time of clinical latency between diagnosis and onset of psoriasis was about 9.4 (1-19) years and time between the beginning of all biological infusions and the onset of psoriasis was about 7 (3-12) months. 7 of 13 (54%) patients received infliximab, 3 (23%) adalimumab and 3 (23%) certolizumab pegol at onset of psoriasis. In 9 of 13 patients (69%) the anti-TNF-therapy was changed or discontinued. In most of the cases (85%), skin lesions improved or disappeared.

*Conclusion:* Most of our described patients featured a complicated disease course of CD and had an improvement of the rash after changing the anti-TNF-therapy. This is in line with available literature.

**Key Words:** Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, anti-TNF-agents, Psoriasis, Infliximab, Adalimumab, Certolizumab, Golimumab.

## INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract (GIT), which includes Crohn's disease (CD) and ulcerative colitis (UC). While UC is restricted to the colon and reflects a continuous inflammation confined to the mucosal layer, CD is characterized by a discontinuous, granulomatous and transmural inflammation that can occur anywhere in the GIT. Environmental, genetic and immunological factors as well as the intestinal microbiota have been considered as the major etiology of IBD. Evidence suggests that an epithelial barrier defect, coupled with a dysfunctional immune response of the innate as well as the acquired immune system to commensal microbiota, resulting in either excessive up- or impaired down-regulation of inflammatory events, drives the development of chronic intestinal inflammation (1). The predispositions are genetically determined and variations in about 160 gene loci have been associated with IBD (2, 3).

Current treatment strategies include steroids, immunosuppressants as well as biologicals, in particular anti-TNF-antibodies. The introduction of anti-TNFs for IBD was in the late 1990s and these agents have proven efficacy in the induction and maintenance of remission in CD and more recently in UC. They are also routinely used in the management of rheumatologic conditions (e.g. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis) and psoriasis (4). Infliximab was the first biologic agent targeting TNF, and was followed by other anti-TNF antibodies, such as adalimumab, certolizumab pegol and golimumab. (4-6)

The number of IBD patients being exposed to TNF inhibitors has dramatically increased within the last decade. Though clinical efficacy and safety of anti-TNF agents is well demonstrated, a significant number of patients exhibit side effects that often lead to discontinuation of anti-TNF treatment. This situation then displays a serious problem since further treatment options are limited and often fail.

A certain group of complications under the treatment with anti-TNF antibodies that gains more and more importance in the clinical management of IBD patients is the manifestation of psoriatic skin lesions. This phenomenon is seemingly paradoxical because of anti-TNF agents (e.g. infliximab and adalimumab) are also effective in the treatment of psoriasis (5-7). After publication of the first case series (8, 9), it nowadays appears, that the magnitude of this problem has long been (and probably still is) underestimated.

Besides the unpleasant nature of this dermatopathy, ranging from predominant cosmetic impairment up to severe pruritus and psychological, sexual as well as psychosocial affections, the severe impact of this side effect lies in the fact that a substantial fraction of patient needs either to be switched to an alternative anti-TNF agent (with only limited efficacy) or completely withhold (about 30% of patients) from TNF-inhibitors (4, 9-12) possibly resulting in acute IBD flares.

Here, we describe 13 new cases of CD patients developing psoriasis or psoriasiform skin lesions while being under anti-TNF therapy. This adds significantly to the described number of somewhat over 220 such cases to date. The further purpose of this study was to perform a systematic review of reported cases with this pathology.

## **PATIENTS AND METHODS**

We retrospectively identified 13 cases of anti-TNF-induced psoriasis or psoriasiform skin lesions in patients with CD in the IBD outpatient clinic at the Division of Gastroenterology and Hepatology, University Hospital Zurich, Switzerland between 2007 and 2013. A detailed review of each patient's medical record was undertaken, focusing on demographics, type of IBD, years from diagnosis of CD, presentation, location and behaviour according to the Vienna Classification, personal and family history of psoriasis, time of onset of psoriasis, site of lesions complications, therapy, and outcome. In each case, the tentative diagnosis psoriasis was diagnosed by the gastroenterologist and in most of the cases confirmed by a dermatologist who carried out a biopsy of the respective skin lesions, if deemed necessary.

### **Systematic Review**

A comprehensive search was conducted using MEDLINE and PubMed databases from January 1946 to July 2013. The keywords used were: “Crohn's disease”, “ulcerative colitis”, “inflammatory bowel disease”, “psoriasis”, “psoriatic skin lesion”, “anti-TNF”, “infliximab”, “adalimumab”, “certolizumab pegol” and “golimumab”, either singly or in combination. Reports describing histological types of psoriasis or psoriatic skin lesions in patients that had not been on anti-TNF therapy at time of occurrence were excluded. The reference lists from the relevant articles were also searched manually to identify trials for possible inclusion. All available clinical and pathological variables from these reports were included.

### **Statistical analysis**

The statistical analysis included descriptive statistical analysis. Qualitative variables were expressed as percentages with confidence intervals (CI). The quantitative variables as expressed as the mean and standard deviation or median and interquartile range, according to the presence or absence of a normal distribution.

## **RESULTS**

We identified 13 patients with the diagnosis of CD and a concomitant diagnosis of psoriasis or psoriasiform skin lesion while receiving an anti-TNF-antibody (e.g. adalimumab, infliximab, certolizumab pegol or golimumab). Of note, no such cases in UC patients were found.

### **Demographic aspects**

In this case series all patients had CD. 10 of 13 (77%) patients were female with the diagnosis of CD, a mean age of 26.9 (18-54) years at diagnosis and no personal and/or family history of psoriasis. Three of them (23%) were men, with a mean age of 22 (15-34) years and also without a history of psoriasis. (Table 1)

### **IBD-Characteristics**

Multiple other organ systems can be affected in IBD patients, including the bones and joints, skin and eyes. In our review 8 of 13 patients (62%) with CD had extraintestinal manifestations. All of those 8 patients were suffering from arthritis and 2 of them (25%) additionally had a manifestation of their skin other than psoriasis (both of them had an Erythema nodosum and a Pyoderma gangraenosum). In three patients IBD was associated with arthritis and perianal inflammation (37.5%) or in two patients with arthritis in combination with an association of their bones (25%). Five (38%) CD patients had no extraintestinal manifestation. 6 (46%) CD patients featured a steroid-dependent disease course and 11 of the 13 (85%) CD patients received azathioprine at any stage during their disease.

### **IBD-Complications**

The major intestinal IBD complications include fistulas and stenosis either alone or in combination. In our case series 11 of 13 patients (85%) had a complicated disease characterized either by stenosis or fistulae. Only 2 (15%) CD patients showed an inflammatory, meaning non-stricturing non-penetrating disease course and 3 (23%) patients featured a structuring disease, while the majority of 8 patients (62%) featured a penetrating disease. Of the 13 CD

patients, 1 (8%) patient had inflammation restricted to the terminal ileum and 2 (15%) patients had colonic disease. 10 (77.0%) patients had ileocolonic disease and 2 of them also had upper GI tract involvement (Table 2). In our review 7 of 13 (54%) CD patients had a surgery in their medical history. The mean time of clinical latency between the diagnosis and the first operation was about 7 (1-12) years.

### **Clinical manifestations**

For the treatment of the 13 CD patients, 4 different anti-TNF-antibodies, namely, infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP) and golimumab were used. 11 of 13 (85%) patients had IFX, 8 (62%) patients ADA and 7 (54%) CZP in their medical history. Only one patient was in treatment with golimumab after receiving IFX, ADA and CZP.

In our case series three anti-TNF-agents (IFX, ADA and CZP) were responsible for the induction or exacerbation of psoriasis or psoriasiform lesions in CD patients. At onset of skin lesions, six (46%) patients with CD were in treatment exclusively with IFX, three with ADA (23%) and three with CZP (23%). In one patient IFX as well as CZP were responsible for the induction or exacerbation of the psoriasiform lesions. The mean time of clinical latency between the diagnosis and the onset of psoriasis or psoriasiform skin lesions was about 9.4 (1-19) years. The mean time of clinical latency between the beginning of all biological infusions and the onset of psoriasis or psoriasiform skin lesions was averaged about 7 (3-12) months (Table 3).

9 of the 13 CD patients (69%) that developed psoriasis or psoriasiform skin lesions under the treatment with anti-TNF agents saw a dermatologist and 8 (62%) received a skin biopsy. The skin biopsy results showed features consistent with psoriasis in 3 (37.5%) patients and psoriasiform skin lesions in 5 (62.5%) patients.

The most frequent sites of psoriatic or psoriasiform skin lesions were the limbs (54%) in 7 patients, followed by the scalp (31%) in 4 and the trunk (23%) in 3 patients. Most of them had more than one site of skin lesions (Figure 1).



## **Management**

In 4 of 13 (31%) CD patient current anti-TNF treatment was stopped and switched to a different medication (e.g. methotrexate, steroids or azathioprine). All of them had a topical treatment and in 3 cases they had an improvement of their skin lesions. In 4 (31%) patients the current anti-TNF-agents were switched to another one. All of them also featured an improvement. One patient (8%) was switched first to another anti-TNF-agent but as the dermatopathy had recurrent the patient was switched to an experimental drug (interleukin-6-antibody) and anti-TNF treatment was stopped. In 2 (15%) patients the medication with anti-TNF-agents was continued and not suspended, they had an improvement of their skin lesions under topical treatment with corticosteroids. In another two patients (15%) the final decision about how to go on with anti-TNF-therapy was not made at present. Topical treatment was the anti-psoriatic therapy most often used (85%), in most cases with topical corticosteroid resulting in improvement of skin lesions nearly in all cases.

## DISCUSSION

Since their introduction in the late 1990's, anti-TNF-agents have acquired a prominent place in the treatment of IBD and psoriasis (4). Paradoxically, numerous reports of new onset or exacerbation of psoriasis under treatment with anti-TNF-agents have been observed in patients with IBD. Although the first case of anti-TNF-agent (IFX) induced psoriatic lesions was described in a patient with CD (13), most of the concerning skin lesions were obtained from the rheumatologic literature (14). An increasing number of IBD patients developed a psoriasis skin lesion as described in numerous reviews (15-17) and the latest overview in patients with IBD mentions more than 220 cases (18).

In our case series representing 13 new cases, we found that all of the patients with anti-TNF-agents induced psoriasis or psoriasiform skin lesions were patients with CD without a personal history of psoriasis. This observation is in good accordance with previous data in the literature where CD patients are also described to be mainly affected. However, to our surprise we did not find any UC patients featuring such a pathology in our outpatient clinic (18) (16) (19). In our experience, CD patients developing psoriasis or psoriasiform skin lesions were mainly female with CD (77%), while in the literature the male:female ratio seems to be mainly equivalent.

In literature, it is recommended that patients developing psoriasis or psoriasiform skin lesions while receiving anti-TNF-therapy should be evaluated by a dermatologist (20, 21). In our case series 9 patients (69%) saw a dermatologist and 8 (62%) had a skin biopsy. Their histopathological assessments revealed the diagnosis of a psoriasiform lesion in 5 (62.5%) patients as the most reported form of skin lesions and the diagnosis of psoriasis in the biopsy of 3 (37.5%) patients. In the other cases the skin lesions were described as a psoriasiform lesion. Because there is no exact and clear definition of psoriasiform or psoriasis-like lesions, many of these cutaneous reactions may actually be the classic type of psoriasis. However, to classify and diagnose the respective skin lesions accurately and to initiate adequate treatment, it might be the best option that patients who developed psoriasis or psoriasiform skin lesions while undergoing anti-TNF-therapy should be evaluated by a dermatologist (20, 21).

Our observed sites of psoriasis or psoriasiform skin lesions by patients with CD were the limbs in 7 patients (54%), followed by the scalp (31%) in 4 and the trunk (23%) in 3 patients. This is also in accordance to other reviews (16, 19).

Multiple other organ systems can be affected in IBD patients, including the bones and joints, skin and eyes (22, 23). In our case series 8 of 13 (62%) patients had extraintestinal manifestations; all of them had IBD-associated arthritis/arthropathy. Two patients (25%) also had a manifestation of their skins (both of them had an erythema nodosum and a pyoderma gangraenosum) and two patients a manifestations of their bones (25%). This is also well in line with previous findings (24, 25).

The multitude of perianal complications in CD patients includes fissures, fistulas, abscesses, and stenosis either alone or in combination. In our case series 85% patients had a complicated disease characterized either by stenosis or fistulae. The medical therapy is considered to be the treatment modality of choice for most IBD patients while operative management is reserved for individuals who fail medical treatment or develop potentially life-threatening complications. However, most patients with IBD ultimately require one or more operations over their lifetime. In our review 7 of 13 (54%) CD patients had a surgery in their medical history with a mean time of clinical latency between the diagnosis and the first operation of 7 (1-12) years. Previous studies have shown similar results (26-28).

In our case series 13 patients with CD had been treated with 4 different anti-TNF-agents, infliximab (IFX), adalimumab (ADA), certolizumab (CZP) or golimumab and three of them (except golimumab) were responsible for the induction or exacerbation of psoriasis or psoriasiform lesions in our case. Most of the patients (54%) received IFX. This observation is in good accordance to other literature (16, 18, 19). The majority of the infliximab-therapy likely reflects the fact that it was the first biological agent available on the market and because of that the drug has been used longer than the other anti-TNF-agents.

The duration of anti-TNF-therapy prior to the onset of the rash is highly variable suggesting that an environmental trigger may also be involved (16, 18). The mean time of clinical latency between the diagnosis and the onset of all biological infusions was about 9.4 (1-19) years and the mean time between the beginning of the biological-therapy and the onset of psoriasis or psoriasiform skin lesions in our case series was about 7 (3-12) months.

At this time no guideline exists for treating the psoriasis or psoriasiform skin lesions in patient with IBD under treatment with anti-TNF-agents. There is a wide range of therapeutic approaches, but there is a disagreement whether discontinuation of the biological is needed to achieve an improvement or complete resolution of the lesions (16, 18).

In our patient collective, anti-TNF treatment was either stopped and the patient was switched to a different, non-anti-TNF medication (e.g. methotrexate, steroids or azathioprine), anti-TNF-agents were switched to another one or the anti-TNF-agents were continued and not suspended. Of note, all of those three approaches were successful, at least in some of the patients and/or in combination with specific psoriasis treatment. Topical steroids are the treatment of choice for the skin lesions alone or in combination with other topical drugs or phototherapy. In our case series, 85% had a topical treatment, mostly with topical steroids and most of our patients showed an improvement of skin lesions.

Although psoriatic lesions that are induced or exacerbated by anti-TNF-agents in patients with IBD have been reported, their immunopathogenetic mechanism has not yet been elucidated (15, 18). It is known that T-cells play a key role for the development of chronic inflammatory conditions such as IBD, psoriasis, rheumatoid arthritis (RA) or systemic lupus erythematoses (SLE).

Due to the surprising nature of this induced dermopathy, as anti-TNF agents are also largely and successfully used in the treatment of psoriasis, the term paradoxical psoriasis has been coined. To date, the pathogenesis of such psoriatic lesions occurring under anti-TNF therapy still largely remains obscure. All in all, the direct mechanism of action of these agents, namely neutralization of TNF, most likely is a key element in the pathogenesis. A dysbalance between TNF and interferon (IFN)  $\alpha$  seems to be of great importance (32). IFN $\alpha$  is produced in dermal plasmacytoid dendritic cells (pDCs), is negatively regulated by TNF (33) and is known as a key driving factor in the pathogenesis of psoriatic skin lesions development (34, 35). However, other cytokine and T-cell pathways were also identified as potential key-players and this was mainly driven by the recognized overlap of candidate genes in IBD on the one and psoriasis as well as eczema on the other hand (36, 37). Nevertheless, the rising number of IBD patients developing psoriatic skin lesions under anti-TNF therapy makes the need for further investigation about the pathogenetic of these complications obvious. A better pathogenetic understanding would clearly help to define and improve treatment strategies for this complication.

All in all, we show that psoriatic skin lesions in CD patients under anti-TNF therapy occur mainly in females featuring a complicated disease course. Since these patients are obviously difficult to treat anyway, the onset of psoriatic skin lesions makes their treatment even more difficult. Therefore, our study might contribute to better characterization of these patients class.

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## Tables:

**Table 1:** Summary of demographic characteristics of 13 CD patients with psoriatic lesions induced or exacerbated by anti-TNF-agents. CD: Crohn's disease, PS: psoriasis

Variables	Patients (No. = 13)
Primary disease, no. (%)	
CD	13 (100)
Gender, no. (%)	
Female	10 (77)
Male	3 (33)
Median age at diagnosis (years)	26.9 (18-54)
Previous history of PS, no. (%)	
No (de novo or induced PS)	13 (100)
Personal (exacerbated pre-existing PS)	

**Table 2:** Vienna Classification in 13 CD patients. In according to the Vienna Classification: A (Age at diagnosis): A1:<40 years, A2:>40 years. L (Location): L1: terminals Ileum, L2: Colon, L3: Ileocolon, L4 Upper GI. B (Behavior): B1: nonstricturing, nonpenetrating, B2: Stricturing, B3: Penetrating.

	A1	B1	B2	B3	A2	B1	B2	B3
L1				1 (8%)				
L2				1 (8%)	1 (8%)			
L3			2 (15%)	6 (45%)				
L3/4	1 (8%)			1 (8%)				

**Table 3:** Summary of data of 13 CD patients with psoriatic lesions induced or exacerbated by anti-TNF-agents. IBD: inflammatory bowel disease. CD: Crohn's disease. TNF: tumor necrosis factor.

	Patients (No. = 13)
Female, n (%)	10 (77)
Male, n (%)	3 (33)
Median age at diagnosis in years	26.9 (18-54)
New onset of skin lesion, n (%)	13 (100)
Personal history of psoriasis (%)	
CD, n (%)	13 (100)
Anti-TNF treatment used at the time of skin lesion	
Infliximab (%)	7 (54)
Adalimumab (%)	3 (23)
Certolizumab (%)	3 (23)
Median time from diagnosis to onset of rash (range) in years	9.4 (1-19)
Median time from start of anti-TNF to onset of rash (range) in months	7 (3-12)
Infliximab	8,7 (2-12)
Adalimumab	6 (3-9)
Certolizumab	4 (4-4)



**Figure:**

**Figure 1:** Examples of TNF-induced psoriasis lesions

Locations: 1. limbs, 2+3. palmoplantar, 4. trunk, 5. Manifestation of the skin: pyoderma gangraenosa

